REMARKS

Claims 1-4, 6-13, 16-19 and 36-47 were examined. In the instant Office Action, the Examiner has raised the following issues, which are set forth by number below in the order they are addressed herein:

1) Claims 2-4 and 8 stand rejected under 35 USC § 112, second paragraph, as allegedly being indefinite;
2) Claims 1-4, 6-12, 16-19, 36 and 37 stand rejected under 35 USC § 103(a), as allegedly unpatentable over Pumpens *et al., Intervirology,* 38:63-74, 1995 (Pumpens);
3) Claim 13 stands rejected under 35 USC § 103(a), as allegedly being unpatentable over Pumpens, in view of Zlotnick *et al., Proc Natl Acad Sci USA,* 94:9556-9561, 1997 (Zlotnick);
4) Claims 42-47 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement;
5) Claims 1-4, 6-13, 16 and 17 stand rejected under 35 USC § 112, first paragraph, as allegedly lacking enablement; and
6) Claims 38-41 stand rejected under 35 USC § 112, first paragraph, as allegedly lacking enablement.

Applicants thank the Examiner for withdrawal of the objection and several rejections of the previous Office Action. Even so, Applicants hereby amend Claims 1-3, 8, 18, 36, 38 and 39, cancel Claims 4, 6, 7, 9, 21-24 and 40-47, and enter new Claims 48-58, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments. Applicants reserve the right to prosecute the original, similar, or broader claims in one or more future application(s). These amendments do not introduce new matter.

1) The Claims Are Definite

The Examiner has rejected Claims 2-4 and 8 under 35 USC § 112, second paragraph, as allegedly being indefinite. Briefly, the Examiner has rejected the claims for reciting "a loop

region comprising residues 76 to 82 of SEQ ID NO:38" (Office Action, page 3). Although Applicants respectfully disagree with this rejection, Applicants have deleted the phrase "loop region" from Claims 2-4 and 8, thereby rendering this rejection moot.

2 & 3) The Claims Are Nonobvious

The Examiner has rejected Claims 1-4, 6-12, 16-19, 36 and 37 under 35 USC § 103(a), as allegedly unpatentable over Pumpens *et al., Intervirology,* 38:63-74, 1995 (Pumpens), and has rejected Claim 13 as allegedly unpatentable over Pumpens in view of Zlotnick *et al., Proc Natl Acad Sci USA,* 94:9556-9561, 1997 (Zlotnick). The Examiner states that:

> Pumpens teaches strong conservation among hepatitis core antigens (hepatitis: as well as between mammalian core proteins and avian hepadnaviruses) and even more specifically with woodchuck hepatitis core antigens (p. 64, Pumpens; as further supported by US 2003/0138769 A1 in the previous Office Action, and Lew et al. (2001) as cited in the Form 1449 dated Oct. 31, 2003). There is no minimum percentage of homology required between hepatitis core antigens to be interchangeable or not, while 66% indicates more homology than not. In addition the standard is a "reasonable" (emphasis added) expectation of success, not inadequate. Furthermore, applicant's own disclosure posits to some differences, but even alleges they are interchangeable and substitutable and furthermore, woodchuck hepatitis core antigens offer certain advantages.
>
> Second, Pumpens teaches insertions within these ranges (see Tables 103, Pumpens). Unless applicant shows unexpected results for insertions at the residue positions recited in the claims, Pumpens is presumed to apply and the rejection stands for reasons of record (Office Action, page 6).

To begin with the Examiner is reminded that to reach a proper determination of obviousness, that the:

> examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. ... Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art (MPEP 2143).

Applicants' contend that the Examiner is improperly relying on the Specification in his unsuccessful attempt to establish a *prima facie* case of obviousness. Applicants respectfully submit the Examiner has not established all elements of a *prima facie* case of obviousness and has failed to fully address Applicants' arguments from the previous response.

(a) No Suggestion or Motivation to Modify the Reference(s)

The Examiner is also reminded that the mere fact that the reference(s) can be modified does not render the resultant modification obvious, unless the prior art also suggests the desirability of the modification.[1] In the first place, Pumpens simply discloses that there is conservation between the protein sequence of human hepatitis B core antigens (HBcAg) and the core antigens of other mammalian hepadnaviruses. Pumpens does not teach or suggest that woodchuck hepadna virus core antigens (WHcAg) can be substituted for HBcAg for the purpose of producing an epitope carrier. However, the pending claims are directed to WHcAg with insertions at 17 specific positions, only four of which are identical to the corresponding HBcAg positions (e.g., ~24%). Importantly, many of the recited positions are within or adjacent to the immunodominant loop residues 76-82, where the amino acid sequence identity is virtually non-existent (*e.g.*, ~14% corresponding to 1 of 7 shared residues). Applicants respectfully assert that the Examiner must provide evidence to support his contention that there "is no minimum percentage homology required between hepatitis core antigens to be interchangeable or not" (Office Action, page 6). Under the law

> "assertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific `knowledge' of the prior art, which might be peculiar to a particular art should also be supported" (MPEP 2144.03).

Additionally, Applicants respectfully remind the Examiner that the pending claims recite that the hybrid woodchuck hepadnavirus core antigens (WHcAg) are antigenic. In regards to antigenicity, Applicants teach that

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[1] *See, In re Mills,* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

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> the WHcAg and the HBcAg do not significantly crossreact at the antibody (B cell) level (*See,* Figure 6) and are only partially crossreactive at the $CD4^+$ T helper cell level (*See,* Figures 7-10). ... Crossreactivity between anti-WHc and anti-HBc antibodies ranged between 0 and 0.8%. Similarly a panel of monoclonal antibodies (mAb) specific for the HBcAg was found to be totally non-crossreactive with the WHcAg when tested for binding to solid phase HBcAg and WHcAg by ELISA. The anti-HBcAg mAb panel included #3105, #3120 (Takashi *et al.*, J.Immunol, 130:2903-2911, 1983), C1-5 (Chemicon, Temicula, CA), C3-1, #440 and #442 (Boehringer Mannheim, Germany), and H40-C47. ... Also note the low level of crossreactivity between the WHcAg and the HBcAg [at the Th cell level]. Specifically, the HBcAg required an *in vitro* concentration of 80 ng/ml to recall a proliferative response from WHcAg-primed T cells which amounts to a 666-fold difference from the recall response observed for WHcAg. This result and additional studies indicate that the WHcAg-primed T cells in Balb/c mice ($H\text{-}2^d$) recognize a site(s) on WHcAg which is not conserved on the HBcAg (Examples 4 and 5 of Specification, from page 89, line 14 to page 92, line 21.

Hence, HBcAg and WHcAg proteins are not well conserved in the primary amino acid sequence within or adjacent to the immunodominant loop, or in terms of antigenicity. As such one skilled in the art would not be motivated to substitute WHcAg for HBcAg.

(b) No Reasonable Expectation of Success

Applicants submit that the Examiner has simply set forth an argument that it would be "obvious to try" to develop the presently claimed invention. However, this is a standard that has been thoroughly discredited. "Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful."[2] Prior to development of the combinatorial technology disclosed in the present Application, a significant proportion of hybrid HBcAg (as well as WHcAg) particles could not be produced due to well-known problems in particle expression and assembly (Jegerlehner *et al., Vaccine*, 20:3104-3112, 2002 and Karpenko *et al., Amino Acids,* 18:329-337, 2000).

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[2] Quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 (Fed. Cir. 1989).

The Examiner is reminded to:

> consider any teaching or suggestion in the reference for a preferred species or subgenus that is *significantly* different in structure from the claimed species or subgenus. Such a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness (MPEP, 2144.08.II.A.4(c), emphasis added).

To this end, Pumpens teaches away from the claimed invention:

> N- and C-terminal regions, as well as the immunodominant loop in the middle of the molecule are widely accepted as targets for the introduction of foreign epitopes, ensuring retention and even enhancement of the original immunological activity of the inserted sequences (Pumpens, abstract).

Importantly, as discussed above the conservation of immunodominant loop sequence between HBcAg ayw and WHcAg is virtually non-existent (*e.g.,* 14% corresponding to 1 of 7 shared residues). Applicants submit that this low level of homology surely does not provide a reasonable expectation of success in achieving WHcAg cores containing inserts within or adjacent to the immunodominant loop and that assemble as antigenic hybrid particles (e.g., embodiments of Claims 3, 8, and 48-58).

(c) No Teaching or Suggestion of All Claim Limitations

Although Applicants respectfully disagree that the claims are obvious, Applicants have entered new Claims 48-58, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s). Specifically, new Claims 48-58 are directed to embodiments in which the heterologous antigen is inserted at one of the following positions of the truncated WHcAg core: amino acid residue 44, 71, 72, 73, 74, 75, 76, 83, 84, 85 or 92. Support for the recited insert positions are found in the text of original Claims 3, 4, 6 and 7, among other locations.

In regard to new Claims 48-58, both Pumpens and Zlotnick fail to teach or suggest the insertion of a heterologous antigen at any one of these positions of HBcAg. In fact, the only insert positions disclosed by Pumpens that did not entail a deletion of HBcAg immunodominant loop residues were at amino acid residues 77, 78, 81 and 82. Similarly in regard to Claim 13 (as

well as withdrawn Claims 14 and 15) both Pumpens and Zlotnick fail to teach or suggest a truncated WHcAg further comprising any of the recited artificial C-termini.

As the Examiner has not established a *prima facie* case of obviousness with his combination of Pumpens and Zlotnick, Applicants respectfully request that these rejections be withdrawn.

4) The Claims Meet The Written Description Requirement

The Examiner has rejected Claims 42-47 under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement for defining the heterologous antigen only in terms of its isoelectric point (Office Action, pages 7 and 8). Although Applicants respectfully disagree with this rejection, Applicants have canceled Claims 42-47 without prejudice, thereby rendering this rejection moot.

5) The Claims Are Enabled

The Examiner has rejected Claims 1-4, 6-13, 16 and 17 under 35 USC § 112, first paragraph, as allegedly lacking enablement. In particular the Examiner states that:

> the specification while being enabling for an antigenic composition comprising an antigen linked to SEQ ID NO:38 wherein said heterologous antigen is inserted at positions such as 44, 73-78 and 81-85, 92 does not reasonably provide enablement for the entire scope of amino acid residues comprising 76 to 82 (in other words, even further components, since the claims comprise 76 to 82 and are not even limited to residues 76-82).
>
> Applicant's disclosure does contain examples of certain inserts at position 78 that have provided stable particle assembly upon C terminal modification (see specification; Tables 11-16 indicating successful particle recovery for specific inserts; satisfactory assembly immunogenicity). However, the disclosure does not sufficiently teach enough beyond those specific residue positions at 44, 73-78 and 81-85, 92 or specific inserts to enable the entire scope of the range and scope of foreign epitopes or antigens. Applicant's own disclosure even teaches a screening method on p. 96 to determine efficacy of expression and assembly of hybrid cores particles at the early bacterial lysate step, in effect indicating that screening is required because of the limited certainty in moving from one species to another (Office Action, pages 9 and 10).

Although Applicants respectfully disagree with this rejection, Applicants have amended Claims 1, 2, 3 and 8, 18 and 36, canceled Claims 4, 6, 7, 9, and entered new Claims 48-58, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s). Specifically, Applicants have amended Claims 1, 18 and 36 to recite "wherein said heterologous antigen is 50 or fewer amino acids in length and is inserted at a position chosen from amino acid residues 44, 71, 72, 73, 74, 75, 76, 77, 78, 81, 82, 83, 84, 85, 92, N-terminal or C-terminal of SEQ ID NO:38." Likewise Claims 2, 3, and 8 have been amended, while new Claims 48-58 have been drafted to recite subsets of these positions. Support for the recited insert positions are found in the text of original Claims 3, 4, 6 and 7, among other locations. In addition, support for a heterologous antigen of 50 or fewer amino acid residues is provided by the definition of "antigen" as exemplified by "molecules which contain a peptide," and by the definition of "peptide" as encompassing molecules containing from two (2) to about fifty (50) amino acids (Specification, page 39, lines 18-25). Applicants' successful production of hybrid woodchuck hepadnavirus core particles containing heterologous antigens at all of the recited positions clearly provides enablement commensurate with the scope of the amended claims.

The Examiner is respectfully reminded that an Applicants' indication that some screening may be required to determine where a heterologous antigen in question will be tolerated in the context of any given artificial C-terminus in and of itself is not indicative of a lack of enablement. In particular the

> quantity of experimentation needed to be performed by one skilled in the art is only one factor involved in determining whether "undue experimentation" is required to make and use the invention. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). MPEP 2164.06.

Applicants' contend that the screening methods of the Specification provide more than sufficient guidance to put a skilled artisan in possession of the scope of the invention as presently claimed. Accordingly, Applicants respectfully request that this rejection be withdrawn.

6. The Claims Are Enabled

The Examiner has rejected Claims 38-41 under 35 USC § 112, first paragraph, as allegedly lacking enablement. The Examiner states that

> the specification while being enabling for the rescue of hybrid particles with certain positively charged inserts using flanking glutamic acid residues, does not reasonably provide enablement for other antigenic acidic amino acid additions or substitutions or insertions or insertions or substitutions within said amino acid sequence.
>
> Applicant's disclosure contains examples of the use of flanking glutamic acid residues in Table 18 for specific inserts where the addition of the acidic amino acid residues created successful hybrid particle recovery. However, the disclosure does not sufficiently teach enough beyond that for other acidic amino acid residues (aspartic acid), or for any inserts not specifically mentioned, which comprise a broad variety of antigens and foreign epitopes (Office Action, pages 11 and 12).

Applicants respectfully disagree with this rejection. Nonetheless Applicants have amended Claims 38 and 39, and canceled Claims 40 and 41, in order to further the prosecution of the present application and Applicants' business interests, yet without acquiescing to the Examiner's arguments, and while reserving the right to prosecute the original, similar, or broader claims in one or more future application(s). Specifically, Applicants have amended Claims 38 and 39 to recite "further comprising flanking glutamic acid residues," and "further comprising flanking aspartic acid residues," respectively. Support for this amendment can be found but is not limited to Example 15, which teaches that both flanking glutamic acid residues and flanking aspartic acid residues rescued a positively charged heterologous antigen (Specification, page 109, lines 17-30). Applicants assert that the amended claims are enabled and accordingly request that this rejection be withdrawn.

CONCLUSION

Applicants believe the amendments and arguments set forth above traverse the Examiner's rejections and, therefore request that a timely Notice of Allowance be issued in this case. However, should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect before the mailing of a further Office Action.

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